Hypercholesterolemia Induced by Cholesterol- or Cystine-Enriched Diets Is Characterized by Different Plasma Lipoprotein and Apolipoprotein Concentrations in Rats\(^1,2\)

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ABSTRACT This study examined the effects of diet-induced hypercholesterolemia on plasma apolipoprotein (apo) concentrations and hepatic apolipoprotein mRNA levels in rats. Hypercholesterolemia was induced by feeding rats diets containing an excess of either cholesterol or cystine. After cholesterol feeding, plasma apo E and apo B concentrations were lower (−85%, \(P < 0.001\)) and greater (+39%, \(P < 0.01\)), respectively, compared with control diet-fed rats. After cystine feeding, plasma apo B and apo E concentrations were greater (+46%, \(P < 0.01\) and +75%, \(P < 0.001\), respectively) and plasma apo A-IV concentration was lower (−29%, \(P < 0.001\)) than in rats fed control diet. After cholesterol or cystine feeding, a tendency (one-way ANOVA, \(P = 0.08\)) for greater apo B mRNA level (+42% and +47%, respectively) was observed compared with control diet-fed rats. No difference emerged between groups for apo E and apo A-I mRNA levels. An opposite effect of cholesterol and cystine feeding was shown for apo A-IV mRNA level, i.e., higher after cholesterol feeding (+47%, \(P < 0.05\)) and lower after cystine feeding (−65%, \(P < 0.01\)). From this work, it seems that hypercholesterolemia induced by dietary cholesterol or by increased cholesterogenesis in cystine-fed rats is characterized by different plasma lipoprotein and apolipoprotein concentrations and is associated with different apolipoprotein gene expression in the liver. J. Nutr. 125: 35–41, 1995.

INDEXING KEY WORDS:  
- gene expression  
- rats  
- liver  
- apolipoproteins  
- cholesterol  
- cystine

Hypercholesterolemia in humans is frequently related to an increased risk for atherosclerosis. Hyperlipidemic diets have considerable effects on plasma lipoprotein and apolipoprotein concentrations (Grundy and Denke 1990). As a model for diet-induced hypercholesterolemia, the effect of dietary cholesterol on lipoprotein and apolipoprotein metabolism has been extensively studied in various species, both in vivo and in vitro (Grundy and Denke 1990). It has been shown that this source of cholesterol affects apolipoprotein (apo) synthesis in several tissues and that part of this effect may be attributed to modifications in specific apo mRNA levels (Dixon and Ginsberg 1992). Thus, it seems that cholesterol availability may be important in regulating apolipoprotein synthesis. There are several functional pools of cholesterol in the hepatocyte (Suckling and Stange 1985). However, the influence of modifications in cholesterol distribution among various pools on apolipoprotein synthesis has not been reported. In contrast to cholesterol-induced hypercholesterolemia, hypercholesterolemia resulting from enhanced cholesterogenesis has been studied to a lesser extent.

Identification of mechanisms by which dietary or newly synthesized cholesterol regulates apolipoprotein synthesis would provide a better understanding of lipoprotein metabolism. Thus, the present study was designed to determine whether two different hypercholesterolemic conditions—the first induced by providing excess dietary cholesterol and the second induced by feeding rats a diet containing excess cystine—could alter the concentration of plasma apolipoproteins and whether these alterations were mediated through effects upon hepatic apolipoprotein gene expression. We previously

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showed that cystine-enriched diet induces hypercholesterolemia resulting from enhanced cholesterol-ogenesis in the liver [Sérougne et al. 1987].

MATERIALS AND METHODS

Animals, diets and experimental design. Male Wistar rats (Elevage Janvier, Le Genest-St. Isle, France) weighing ~250 g were fed a control diet (Table 1). When rats reached 350 g, they were randomized into three groups of eight animals and each fed for 8 wk either the control diet (control group), the control diet supplemented with 5% l-cystine (cystine group) or the control diet supplemented with 1% cholesterol (cholesterol group). Rats were individually housed in wire-bottomed cages in a temperature-controlled room (22°C) with the dark period from 2000 to 0800 h. Rats were killed by aortic puncture under pentobarbital anesthesia at 1000 h after maximal food consumption during the dark period. Blood was drawn on EDTA (1 g/L). Liver samples (~0.5 g) were rapidly excised and stored at ~80°C for further mRNA analyses. Other liver samples (~1 g) were poured into cold saline buffer (50 mmol/L Tris, 0.3 mol/L D(+)-sucrose, 10 mmol/L dithiothreitol, 10 mmol/L EDTA, 50 mmol/L NaCl, pH 7.4) before microsome isolation for measurement of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (EC 1.1.1.34) activity. All procedures were in accord with the Institute's guide for the care and use of laboratory animals.

Lipoprotein isolation. Plasma was separated from blood cells by centrifugation (2200 × g, 15 min, 4°C) and was adjusted to 1.21 kg/L with solid KBr. A density gradient method adapted from Terpstra et al. (1981) was used to separate lipoproteins. Ultracentrifugation was performed for 24 h at 200,000 × g in a Beckman L8 70 centrifuge (Beckman, Fullerton, CA) using an SW41 rotor at 15°C. Twenty-two lipoprotein fractions were collected for each plasma sample. A control tube containing only saline solutions was also centrifuged and used to determine the density of fractions by refractometry.

Chemical analyses. Total cholesterol, triglyceride and phospholipid concentrations of plasma were assayed in an autoanalyzer (Abbot, Irving, TX) using routine enzymatic procedures (cholesterol: CHOD-PAP, Boehringer, Mannheim, Germany; triglycerides: N, Wako, Biolyon, Dardilly, France; phospholipids: B, Wako). The 22 lipoprotein fractions from each rat were assayed as above for their cholesterol concentration. Cholesterol and triglyceride concentrations in the liver were measured using enzymatic kits (cholesterol: CHOD-PAP, Boehringer; triglycerides: N, Wako, Biolyon) after extracting lipids twice in isopropanol warmed for 1 h at 60°C from liver samples homogenized in isopropanol.

Determination of hepatic hydroxymethylglutaryl (HMG)-CoA reductase activity. Liver microsomes were prepared by the method of Einarsson et al. (1986), immediately frozen in liquid nitrogen and stored at ~80°C. The total microsomal HMG-CoA reductase activity was measured by the method of Rodwell et al. (1976).

Plasma apolipoprotein analysis. Plasma apolipoprotein concentrations were determined by radial immunodiffusion using sheep anti-rat apolipoprotein antisera as previously described (Felgines et al. 1994). Respective lipoprotein fractions obtained from individual rats were pooled for each experimental group before immunoblot study. Fraction samples (16 μL of each) were electrophoresed on 7.5% SDS-PAGE and subsequently electroblotted (Towbin et al. 1979) to a nitrocellulose membrane (Hybond-C-Super, Amersham, Buckinghamshire, U.K.). Immunostaining was performed by using sheep anti-rat apolipoprotein (apo) E antiserum as a first antibody and anti-sheep IgG peroxidase conjugate (Sigma, Saint Quentin Fallavier, France) as a second antibody. The color reaction was developed using 4-chloro-1-napthol (Sigma) as the chromogenic substrate.

Detection of apolipoprotein and β-actin mRNA levels in the liver. Total cellular RNA from liver tissue was isolated using the guanidinium-phenol-chloroform method (Chomczynski and Sacchi 1987). RNA was quantified by measuring the absorbance at
260 nm. RNA integrity was systematically assessed by agarose gel electrophoresis and visualization of 18S and 28S ribosomal RNA by ethidium bromide staining. Aliquots of total RNA were subjected to Northern blot analysis. For quantification of apolipoprotein and actin mRNA abundance, serially diluted aliquots of total RNA (1.25–5 µg) were applied to nylon filters [Nylon Highbond N°, Amersham] using a dot blot apparatus. Rat apo B and apo E and mouse β-actin cDNA probes [kindly provided by P. Cardot, URA CNRS 1283, Paris, France] and oligonucleotide probes for apo A-I and apo A-IV were used to detect specific mRNA as described by Ribeiro et al. [1991] and Seishima et al. [1991], respectively. Restriction enzymes, nick translation kit, random primed DNA labeling kit and T4 polynucleotide kinase were purchased from Boehringer label nucleotides [α32P]dATP and [γ32P]ATP were from Amersham. The presence of an equal amount of total RNA was checked by hybridizing the filters with mouse 18S rRNA cDNA probe [kindly provided by G. Veyssiére, Université Blaise Pascal, Clermont-Ferrand, France] as control. The filters were blotted dry, and autoradiography was performed with intensifying screens at −80°C. Quantification of the relative amounts of specific mRNA was performed by densitometric analysis of the hybridization signal using a laser densitometer (Ultrascan XL, LKB, Bromma, Sweden). Densities of the hybridization signals were plotted against micrograms of RNA applied, and the slope was measured. Relative abundance of apolipoprotein and actin mRNA was expressed as the apolipoprotein or actin mRNA slope/18S rRNA slope ratios.

Statistics. Results are expressed as means ± SEM. The differences between the groups were analyzed using a one-way ANOVA. Following a significant F test (P < 0.05), the Student-Newman-Keuls test was used to identify differences between individual groups. The differences were considered significant at P < 0.05. All statistical analyses were conducted using a statistical computer program [Instat, GraphPad Software, San Diego, CA] on a Macintosh LC computer.

RESULTS

Body weight and food intake. The final body weights measured after 2 mo of feeding, and the daily food intakes were lower in cystine-fed rats than in control rats [Table 2]. No difference was found between cholesterol-fed and control rats.

Plasma lipids and apolipoproteins. Plasma cholesterol concentrations were increased by cholesterol consumption (+67%) and cystine consumption (+52%) [Table 3]. Plasma triglyceride concentrations were decreased by both diets (−39 and −87%, respectively). Plasma phospholipid concentration were similar in these three groups. The measurement of apolipoprotein concentrations in plasma showed higher apo B (+46%) and apo E (+75%) and lower apo A-IV (−29%) concentrations in cystine-fed rats than in control rats. After cholesterol consumption, lower plasma apo E (−65%) and greater plasma apo B concentrations (+39%) were observed. Because plasma apo E concentration was strongly affected by both hypercholesterolemic diets, we studied the concentration of cholesterol and the distribution of apo E by Western blotting in the 22 isolated lipoprotein fractions [Fig. 1a]. Cholesterol concentrations in chylomicrons and VLDL were higher in cholesterol-fed rats and lower in cystine-fed rats than in control animals. In contrast, in the fractions corresponding to HDL1 and HDL2, cholesterol concentrations were higher in cystine-fed rats and lower in cholesterol-fed rats than in the control group. After cystine consumption the distribution of apo E among lipoprotein fractions was slightly broader than in control rats, and no signal appeared in the first fraction in contrast to that which was observed in control rats [Fig. 1b]. In samples from cholesterol-fed rats, apo E was visualized only in the first two fractions.

Hepatic lipids and HMG-CoA reductase activity. Total cholesterol and triglyceride concentrations in the liver were higher in cholesterol-fed rats than in control or cystine-fed rats [Table 4]. Total HMG-CoA reductase activity in liver microsomes was significantly higher (P < 0.05) in cystine-fed rats and lower (P < 0.001) in cholesterol-fed rats than in control rats.

Hepatic apolipoprotein mRNA levels. Apolipoprotein and actin mRNA levels measured in the liver of rats fed control, cholesterol- or cystine-enriched diets are reported in Table 5. After cystine or cholesterol consumption, a tendency (P = 0.08) for greater apo B mRNA expression was observed as compared with control rats. An opposite effect of cystine and cholesterol consumption was shown for apo A-IV mRNA level, which was decreased by cystine-enriched diet and increased by cholesterol-enriched diet. No difference emerged between groups for apo E, apo A-I and actin mRNA levels.

<p>| TABLE 2 |
| Final weight and daily food intake of rats fed for 2 mo the control diet or the control diet supplemented with 5% cystine or 1% cholesterol |</p>
<table>
<thead>
<tr>
<th>Dietary group</th>
<th>Final weight (g)</th>
<th>Daily food intake (g/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>508 ± 12b</td>
<td>18.5 ± 0.4b</td>
</tr>
<tr>
<td>Cystine</td>
<td>432 ± 12b</td>
<td>16.1 ± 0.7b</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>537 ± 14b</td>
<td>18.9 ± 0.8b</td>
</tr>
</tbody>
</table>

Values are means ± SEM of eight rats per group. Values with different letters are significantly different (P < 0.05).
**DISCUSSION**

The aim of this study was to investigate whether the changes in plasma lipoprotein and apolipoprotein concentrations induced by an increased supply of exogenous or endogenous cholesterol are related to changes in apolipoprotein gene expression in the liver. Rats fed diet enriched with 1% cholesterol were used to determine the effects of exogenous cholesterol. Under these conditions, cholesterol synthesis in the liver is extremely low (Sérougne et al. 1987). Rats fed diets enriched with 5% cystine were used to investigate the effects of newly synthesized cholesterol because, under this dietary condition, cholesterol synthesis in the liver is markedly enhanced compared with rats fed the control diet (Sérougne et al. 1987). The present study shows that HMG-CoA reductase activity in the liver is reduced by cholesterol consumption and stimulated by cystine consumption. These results confirm previous data obtained by in vivo [1-14C]acetate incorporation into liver sterols (Sérougne et al. 1987). Moreover, the hepatic cholesterol content was increased by cholesterol feeding and was not modified by cystine feeding.

Cholesterol-fed rats in this study displayed an increase in both plasma apo B and VLDL cholesterol concentrations as previously described (Ross and Zilversmit, 1977, Mathé et al. 1991). Cystine-enriched diet also caused a marked increase in plasma apo B concentration. Compared with control rats in which the relatively high triglyceridermia in fed animals is related to the high sucrose content of the diet, cystine-fed rats displayed very low triglyceridermia, due to very low VLDL concentration. Previous work showed that these low values were correlated with high lipolytic activities (Mathé et al. 1991).

In both groups of hypercholesterolemic rats in the fed state, the higher plasma apo B concentration was accompanied by a tendency toward higher apo B mRNA in the liver. It was previously reported that cholesterol consumption increased apo B mRNA in the liver of rats in the fed state (Matsumoto et al. 1987). However, other data obtained from mice (Srivastava et al. 1991), rabbits (Kroon et al. 1986) and monkeys (Hennessy et al. 1992) in fed or food-deprived conditions have shown no increase in apo B mRNA after cholesterol consumption.

Apolipoprotein B synthesis does not seem to be regulated on short-term basis at the transcriptional level but is rather subjected to post-translational regulation (Dixon and Ginsberg 1992). However, the present work as well as other in vivo and in vitro studies (Dashti 1992, Matsumoto et al. 1987) suggest that when hepatocytes are exposed to an increased supply of exogenous or endogenous cholesterol, apo B synthesis may be regulated at the mRNA level.

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**TABLE 3**

*Plasma lipids and apolipoproteins (apo) in rats fed for 2 mo the control diet or the control diet supplemented with 5% cystine or 1% cholesterol*1

<table>
<thead>
<tr>
<th>Dietary group</th>
<th>Cholesterol</th>
<th>Triglycerides</th>
<th>Phospholipids</th>
<th>Apo B</th>
<th>Apo E</th>
<th>Apo A-I</th>
<th>Apo A-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmol/L</td>
<td>g/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2.40 ± 0.08a</td>
<td>5.21 ± 0.86b</td>
<td>2.80 ± 0.09</td>
<td>0.28 ± 0.02a</td>
<td>0.20 ± 0.02b</td>
<td>0.33 ± 0.01</td>
<td>0.34 ± 0.01b</td>
</tr>
<tr>
<td>Cystine</td>
<td>3.64 ± 0.23b</td>
<td>6.08 ± 0.08a</td>
<td>2.72 ± 0.18</td>
<td>0.41 ± 0.03b</td>
<td>0.35 ± 0.03e</td>
<td>0.32 ± 0.02</td>
<td>0.24 ± 0.02a</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>4.01 ± 0.34b</td>
<td>3.16 ± 0.27h</td>
<td>2.37 ± 0.09</td>
<td>0.39 ± 0.02b</td>
<td>0.07 ± 0.01a</td>
<td>0.32 ± 0.02</td>
<td>0.37 ± 0.03b</td>
</tr>
</tbody>
</table>

1Values are means ± SEM of eight rats per group. Values with different letters are significantly different (P < 0.05).

**TABLE 4**

*Total cholesterol and triglyceride concentrations and total hydroxymethylglutaryl-CoA (HMG-CoA) reductase activity in the liver of rats fed for 2 mo the control diet or the control diet supplemented with 5% cystine or 1% cholesterol*1

<table>
<thead>
<tr>
<th>Dietary group</th>
<th>Total cholesterol</th>
<th>Triglycerides</th>
<th>HMG-CoA reductase activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µmol/g wet wt</td>
<td>µmol/min·mg protein−1</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>6.5 ± 0.4a</td>
<td>19.6 ± 1.4a</td>
<td>77 ± 0.9b</td>
</tr>
<tr>
<td>Cystine</td>
<td>8.4 ± 0.3a</td>
<td>14.6 ± 1.6a</td>
<td>129 ± 19c</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>185.4 ± 19.9b</td>
<td>63.2 ± 4.9b</td>
<td>13 ± 4a</td>
</tr>
</tbody>
</table>

1Values are means ± SEM of eight rats per group. Values with different letters are significantly different (P < 0.05).
The two hypercholesterolemic diets studied have different effects on plasma apo E concentration, which is markedly lower in cholesterol-fed rats and higher in cystine-fed rats than in control rats. In cholesterol-fed rats the low plasma apo E concentration is explained by the fact that apo E is mainly carried by β-VLDL [Ross and Zilversmit 1977], which contains relatively less apo E than does normal VLDL [Sérougne et al. 1984], and by the fact that HDL1, the major apo E-containing lipoprotein class in rats, is practically absent. This situation contrasts with that described in rats fed a cholesterol-rich diet including the hypothyroid drug, propylthiouracil [Mahley and Holcombe 1977] or in other species fed cholesterol-rich diets [Hennessy et al. 1992, Mahley 1978], in which the plasma concentration of apo E is increased. In cystine-fed rats, the high plasma concentration of apo E is due to the increased level of HDL1, because VLDL, although relatively apo E-rich [Sérougne et al. 1984], is present in minute amounts. In the rat, a species devoid of cholesteryl ester transfer protein [Oschry and Eisenberg 1982], HDL1 is generated in plasma from more dense HDL particles that are progressively loaded with cholesteryl esters and enriched in apo E. The surface material released from VLDL lipolysis represents a major source of HDL1 apo E [Gavish et al. 1987, Oschry and Eisenberg 1982]. Therefore, in the present study, the inverse effects of the hypercholesterolemic diets studied on plasma HDL1 concentration could be explained by a reduced HDL1 formation in cholesterol-fed rats and, inversely, by an increased formation in cystine-fed rats. Indeed, the lipolytic activities are reduced in cholesterol-fed rats and stimulated in cystine-fed rats [Mathé et al. 1991]. In addition, the linear relationship between the HDL1 concentrations and HMG-CoA reductase activities in the liver strongly suggests that newly synthesized hepatic cholesterol is involved directly in HDL1 formation. Whether the catabolic processes of apo E-containing lipoproteins contribute to the alteration of their plasma concentrations is not known. Turnover of LDL is not lowered by cholesterol feeding in rats [Bhattacharya et al. 1986], suggesting that the hepatic apo B/E receptor activity is not changed. On the other hand, the apo E receptor(s) seem to be poorly regulated by dietary factors [Jäckle et al. 1992]. Thus, in cholesterol-fed rats, the low concentration of HDL1 is probably related to low formation and the accumulation of β-VLDL to high production rather than to impaired catabolism. In cystine-fed rats, further data are needed to determine whether accumulation of apo E–rich HDL1 results from both impaired catabolism and increased formation.

In any case, the opposite effects of cholesterol- and cystine-enriched diets upon plasma apo E concentrations are not accompanied by changes in apo E mRNA level in the liver. In agreement with our results obtained in fed rats, other authors working on food-deprived animals [Apostolopoulos et al. 1987, Crespo et al. 1990, Go et al. 1988] showed that apo E mRNA levels were not modified in the liver of rats and rabbits fed a cholesterol-rich diet. In contrast, diets containing both cholesterol and propylthiouracil increased hepatic apo E mRNA in rats [Lin-Lee et al. 1981], as observed in monkeys fed cholesterol-rich diets [Hennessy et al. 1992]. In studies on apo E synthesis and secretion, cholesterol consumption increased hepatic apo E production in guinea pigs [Driscoll et al. 1990] and rabbits [Garcia et al. 1984]. In some extrahepatic cells, cholesterol supply regulated apo E synthesis at the transcriptional level [Dixon and Ginsberg 1992]. In contrast, the present study indicates that an increased supply of exogenous or endogenous cholesterol has no significant effect on apo E mRNA level in the liver. Therefore, modifications in apo E synthesis may occur at the post-transcriptional level.

Both studied diets had no effect on apo A-I plasma concentration or hepatic mRNA level. Cholesterol consumption by rats has not been shown to affect apo A-I mRNA level in the liver [Apostolopoulos et al. 1987, Go et al. 1988]. Recent studies using monkeys [Hennessy et al. 1992] and three inbred strains of mice [Srivastava et al. 1992] have also shown that hepatic

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**TABLE 5**

*Apolipoprotein (apo) and actin mRNA levels in liver from rats fed for 2 mo the control diet or the control diet supplemented with 5% cystine or 1% cholesterol*1

<table>
<thead>
<tr>
<th></th>
<th>Apo B</th>
<th>Apo E</th>
<th>Apo A-I</th>
<th>Apo A-IV</th>
<th>Actin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>100 ± 15</td>
<td>100 ± 14</td>
<td>100 ± 9</td>
<td>100 ± 11b</td>
<td>100 ± 8</td>
</tr>
<tr>
<td>Cystine</td>
<td>142 ± 15</td>
<td>94 ± 12</td>
<td>117 ± 11</td>
<td>35 ± 7a</td>
<td>139 ± 8</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>147 ± 14</td>
<td>107 ± 10</td>
<td>99 ± 13</td>
<td>147 ± 18c</td>
<td>117 ± 16</td>
</tr>
</tbody>
</table>

1Values are means ± SEM of 5–8 rats per group. Values with different superscripts were significantly different (P < 0.05). Results are expressed as apolipoprotein or actin mRNA slope/18S rRNA slope ratios.

2Means of results for control diet-fed group were taken as baseline values (100%).
or intestinal apo A-I mRNA does not change after cholesterol consumption. A specific impact of cystine-enriched diet on plasma apo A-IV concentration and apo A-IV mRNA level in the liver was observed in this study. Parallel variations of these two concentrations were also recently observed by Inui et al. (1992) in rats during development and dex-
amethasone treatment. In rats, the intestine is a major site for apo A-IV synthesis; however, changes in liver apoA-IV mRNA level could explain at least in part the observed changes in plasma concentration of this apolipoprotein. In this study, cholesterol-fed rats displayed an increase in apo A-IV mRNA level but without modification in plasma apo A-IV concentration. However, previous studies have demonstrated in food-deprived rats that apo A-IV mRNA level in the liver was not changed by cholesterol consumption (Apostolopoulos et al. 1987, Go et al. 1988). Moreover, results concerning the effect of cholesterol consumption on plasma apo A-IV concentration are divergent because no change or increase was observed (Apostolopoulos et al. 1987, Delamatre and Roheim 1983). Data obtained from cholesterol-fed rabbits in the fed condition have shown an increase in apo A-IV mRNA level without modification in apo A-IV gene transcription, suggesting that dietary cholesterol may affect post-transcriptional events such as mRNA turnover (Crespo et al. 1992). From these observations, we hypothesize that cholesterol consumption increases apo A-IV mRNA level in the liver only when the animals are in the postprandial state.

We have demonstrated that hypercholesterolemia induced by dietary cholesterol or by increased cholesterogenesis in cystine-fed rats is characterized by different plasma lipoprotein and apolipoprotein concentrations and is associated with different apolipoprotein gene expression in the liver.

**FIGURE 1** Cholesterol concentration (means ± SEM of eight rats per group) (top) and apolipoprotein [apo] E distribution [bottom] in gradient density ultracentrifugation-separated lipoprotein fractions in rats fed the control diet, the diet enriched with 5% L-cystine or the diet enriched with 1% cholesterol. Distribution of apo E was visualized by Western blotting as described in Materials and Methods. One-way ANOVA showed significant differences (P < 0.05) in cholesterol concentration in all lipoprotein fractions except fractions 18 and 22. CM = chylomicra.

**LITERATURE CITED**


APOLIPOPROTEINS IN HYPERCHOLESTEROLEMIC RATS


Mathé, D., Séroague, C., Férezou, J. & Lécuyer, B. [1991] Lipolytic activities in rats fed a sucrose-rich diet supplemented with either cystine or cholesterol: relationships with lipoprotein pro-


